PORT PIRIE COHORT STUDY: ENVIRONMENTAL EXPOSURE TO LEAD AND CHILDREN'S ABILITIES AT THE AGE OF FOUR YEARS

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Abstract We studied the effect of environmental exposure to lead on children's abilities at the age of four years in a cohort of 537 children born during 1979 to 1982 to women living in a community situated near a lead smelter. Samples for measuring blood lead levels were obtained from the mothers antenatally, at delivery from the mothers and umbilical cords, and at the ages of 6, 15, and 24 months and then annually from the children. Concurrently, the mothers were interviewed about personal, family, medical, and environmental factors. Maternal intelligence, the home environment, and the children's mental development (as evaluated with use of the McCarthy Scales of Children's Abilities) were formally assessed.

The mean blood lead concentration varied from 0.44 μmol per liter in midpregnancy to a peak of 1.03 μmol per liter at the age of two years. The blood lead concentration at each age, particularly at two and three years, and the integrated postnatal average concentration were inversely related to development at the age of four. Multivariate analysis incorporating many factors in the children's lives indicated that the subjects with an average postnatal blood lead concentration of 1.50 μmol per liter had a general cognitive score 7.2 points lower (95 percent confidence interval, 0.3 to 13.2; mean score, 107.1) than those with an average concentration of 0.50 μmol per liter. Similar deficits occurred in the perceptual-performance and memory scores. Within the range of exposure studied, no threshold dose for an effect of lead was evident.

We conclude that postnatal blood lead concentration is inversely related to cognitive development in children, although one must be circumspect in making causal inferences from studies of this relation, because of the difficulties in defining and controlling confounding effects. (N Engl J Med 1988; 319:468-75.)

ALTHOUGH the health hazards of acute lead toxicity and occupational exposure to lead are well known, uncertainties exist about the adverse effects of environmental exposure to lower levels of lead. Recent epidemiologic studies have indicated that neuropsychological development in children may be impaired by such exposure, but debate persists about methods for ensuring adequate control of the confounding effects of other covariates in such investigations.[1-4]

The early epidemiologic research on the relation between lead and development, which consisted of cross-sectional or case–control studies, was inconclusive. In 1979 Needleman and colleagues, in a community-based study of children in Boston in whom previous exposure to lead was estimated from examinations of deciduous teeth, reported evidence of lead-related neuropsychological deficits.[5] Subsequent research in Germany revealed a similar but statistically insignificant relation.[6] However, in several British studies, adjustment for covariates relating to the social environment greatly attenuated an apparent inverse relation of lead to mental development.[7,8] A recent cross-sectional study of blood lead concentration in relation to cognitive ability and educational attainment in Scottish children six to nine years of age found an inverse relation, with no apparent threshold level of exposure.[9]

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These inconsistent results may have arisen because any effect of environmental exposure to lead on children's development is probably small; many coexistent confounding factors also influence children's development; measurement of antecedent exposure to lead is difficult; and there is uncertainty about the selection and measurement of developmental outcomes. The inconsistencies may also reflect interactive effects, in that the deleterious effects of exposure to lead may be greater in socially disadvantaged children.[4]

To overcome some of these methodologic difficulties, cohort studies have been started in several locations. These investigations are seeking more definitive, prospective evidence of the relation between exposure to lead early in life and subsequent neuropsychological development. In a cohort study of 249 children in Boston, the lead concentration in umbilical-cord blood was inversely related, after adjustment for covariates, to cognitive development assessed every six months up to the age of two years.[1] The effect was most evident in the children in the upper and middle tertiles of blood lead concentrations (i.e., predominantly within the range of 0.3 to 1.0 μmol per liter, or 6 to 21 μg per deciliter).

Debate continues over whether there is a threshold, or "safe," level of exposure to lead. At blood lead concentrations as low as 1.0 μmol per liter, various neurophysiologic and enzymatic processes are impaired,[10,11] and disturbances of heme synthesis and altered central nervous system electrophysiologic responses have even been observed at levels below 0.72 μmol per liter (15 μg per deciliter).[12] Within urban and industrial populations, a substantial proportion of young children may have blood lead concentrations above this level; indeed, within the Port Pirie cohort, the mean concentration at the ages of 15 months

and 24 months exceeds 1.0 μmol per liter (21 μg per deciliter).[13]

The Port Pirie Cohort Study began in 1979. The industrial town of Port Pirie (population, 16,000) is in South Australia, 200 km northwest of Adelaide. The town is situated immediately downwind of a large and longstanding lead-smelting facility, and there is extensive environmental contamination with lead, particularly in topsoil, yard dust, and house dust.[13]

Earlier results from this study have shown considerable individual variation in blood lead concentration during the first four years of life,[13] with approximately one third of the children having levels above 1.21 μmol per liter (25 μg per deciliter) on one or more occasions. Furthermore, postnatal blood lead concentrations have been found to be inversely associated, albeit weakly, with mental development at the age of two years (assessed by the Bayley Mental Development Index), after adjustment for confounding factors.[14]

This paper presents the results of follow-up to the age of four years, when the children's abilities were evaluated with use of the McCarthy Scales of Children's Abilities (MSCA). The MSCA, which can be used in children three to seven years old, comprises five scales: verbal, perceptual performance, quantitative, memory, and motor.[15] The first three of those scales combined form the general cognitive index (GCI). The GCI provides an age-specific index of cognitive functioning. Formal evaluation has shown that the GCI "assesses the child's reasoning, concept formation, and memory when solving verbal and numerical problems and when manipulating concrete materials."[16] An inverse relation has previously been reported between lead concentrations in the teeth of schoolchildren and perceptual–motor functioning[6]; the perceptual-performance scale of the MSCA measures the equivalent function in preschool children.

Methods

From 1979 to 1982 a total of 723 women were recruited during early pregnancy and followed to the live birth of an apparently healthy child.[17] The children were then entered in a long-term postnatal follow-up study. Recruitment was done through the medical practitioners in and around Port Pirie, who, after a series of meetings with the research team, unanimously agreed to support the study. The recruitment rate, estimated from registrations of births during this period, was 90 percent. Of the 548 children who were followed to the age of four, 397 lived in Port Pirie, and 151 were from the immediate rural area, including several smaller towns. The latter 151 children were included to ensure a range of individual blood lead concentrations, and they were found to have lower mean levels than the children from Port Pirie.[13]

The majority (80 percent) of the children lost to follow-up during the four years of postnatal study were in families that left the Port Pirie district; a few families simply discontinued their participation. Follow-up is continuing, and the final detailed formal neuropsychological assessment is being carried out in children who are seven years old.

Blood samples for measurement of lead concentrations were obtained from the pregnant women at specified times and from each child at delivery (umbilical-cord blood) and at ages 6, 15, and 24 months and annually thereafter. The postnatal samples were obtained from capillaries by finger prick, with use of a rigorous cleansing and collection protocol.[18] A pilot study had demonstrated that blood lead concentrations measured in capillary samples were highly correlated with simultaneously determined venous lead concentrations in 47 children in metropolitan Adelaide who were two to four years of age.[19] The samples were obtained by staff members of the Port Pirie Cohort Study. The capillary–venous blood lead correlation coefficient was 0.97.

Blood lead concentration was estimated with electrothermal atomization atomic absorption spectrometry.[20] Measurements of blood lead levels have been performed by our laboratory (at Adelaide Children's Hospital) for more than 20 years. Throughout this study, both internal and external (interlaboratory) quality-control procedures were used, with consistently satisfactory results. A certified commercially prepared product was employed to monitor intrabatch accuracy and to ensure interbatch standardization. External quality control, entailing assays of regularly supplied samples, was ensured by participation in three major programs: the national quality-control program conducted by the Standards Association of Australia and the international programs run by the health department of Pennsylvania and the Wolfson Research Laboratories (Birmingham, United Kingdom). Estimates were standardized to a packed-cell volume of 35 percent for maternal blood, 50 percent for cord blood, and 35 percent for the children's blood.

Each child's cumulative burden of body lead was estimated by trapezoidal integration of the area under the curve of blood lead concentration, according to age (from birth [cord blood sample] to the age of four years). This method of averaging adjusts for the unequal time periods between successive blood samples. Since blood lead concentrations have approximately log-normal distributions, the reported mean blood concentrations of lead are geometric. To reduce the influence of extreme individual values for blood lead concentration on the statistical analyses, the logarithm (base 10) of the concentration was used in all simple and multiple regression analyses.

At the time the blood samples were obtained, the nurse-interviewer also conducted a structured interview to obtain information on a range of demographic, familial, behavioral, medical, and social environmental factors. All interviews were carried out by one of four trained nurse-interviewers.

The developmental status of each child at the age of four years was assessed with use of the MSCA. This assessment and the blood sampling were carried out on different days. A full-time research psychologist who was blinded to the child's past or current blood lead concentration conducted all testing sessions in a clinic setting. Although the psychologist had also assessed the child's development (using the Bayley Scales of Infant Development) at the age of two years, he was not aware of that earlier result when making the subsequent assessment. The conversion of raw-score data to scale scores was done by computer. The scoring process was thus reliable and accurate. Annual mean MSCA scores during the three years of testing were compared in order to test for temporal observer drift; a variation of only 1 percent was found.

Since there are no Australian standardization data on the MSCA, it was not possible to evaluate the absolute scores obtained in our study population. (A review of the original standardization in the United States, from about 1970, might lead one to expect that the scores would be 100 for the GCI and 50 for the other five scales. However, there is evidence that in developed countries, an upward drift in intelligence scores occurs with successive generations.[21]) Since the MSCA was used in this study solely for the epidemiologic purpose of making intracohort comparisons, our results concern only the relative scores for compared groups of children.

Assessment of the care-giving environment, using the Home Observation for Measurement of the Environment (HOME) inventory, was made during a visit to the children's homes when they were three years of age. This inventory evaluates, by means of observations and interviews, the quality of stimulation of children in their homes.[22] The inventory measures processes that mediate the child's development and has six subscales: emotional and verbal responsiveness of the parents; parental acceptance of the child; maternal involvement with the child; organization of the home environment; appropriateness of play materials; and variety in daily stimulation. These aspects of the home environment correlate well with intellectual and verbal development in early childhood.[22,23] One nurse-interviewer who was trained in the use of the HOME inventory made nearly all the assessments, although the first 30 were done by the psychologist-trainer.

Maternal intelligence was estimated with use of the Wechsler

Adult Intelligence Scale–Revised.[24] This test was administered in full by the research psychologist, who was blinded to the children's blood lead concentrations. The testing was done while the children were in the age range of three to five years.

Results

Blood Lead Concentration at Various Ages

The geometric mean antenatal (maternal) blood lead concentration varied from 0.44 μmol per liter (9.1 μg per deciliter) at 16 weeks of gestation to 0.46 μmol per liter (9.5 μg per deciliter) at delivery. The mean lead concentration in blood from the umbilical cord was 0.40 μmol per liter. The mean values in the children at the ages of 6 months, 15 months, and two, three, and four years were 0.70, 1.01, 1.03, 0.94, and 0.79 μmol per liter, respectively. Maximal uptake of lead appears to occur during the second and third years of life. At the age of two years, when the mean blood lead concentration peaked (at 1.03 μmol per liter, or 21.2 μg per deciliter), individual values ranged from 0.24 to 2.75 μmol per liter. There were no postnatal differences in mean blood lead concentrations between boys and girls. The integrated postnatal average blood lead concentration was 0.92 μmol per liter. The distributions of individual values according to age are indicated in Table 1.

Analysis of autocorrelations of blood lead concentration measured at different ages indicated substantial intraindividual "tracking." The estimated Pearson correlation coefficients for all pairs of measures of blood lead concentrations between the ages of 15 months and seven years (with data still incomplete at six and seven years) were in the range of r = 0.55 to 0.80; the value of 0.55 corresponded to the largest possible age difference (69 months). This suggests that for each child, the relative magnitude of the blood lead concentration remained fairly constant with increasing age. This constancy impedes the estimation of the effect of age-specific blood lead concentration on mental development independently of the blood lead concentration at other ages. Correlations between the assessments of lead in the cord blood and postnatal measures were of the order of 0.35 to 0.40.

Results of the MSCA Tests

MSCA testing was completed for 548 children. For 537, it was done within a six-month period around their birthdays, whereas in the other 11, there was an excessive delay before testing. The latter group was excluded from the analysis; among the other 537 children, the time of testing appeared to be unrelated to the blood lead concentration. The mean scores, which were generally higher than the expected values of 100 for the GCI and 50 for other scales, were as follows: verbal, 53.5; perceptual performance, 56.9; quantitative, 50.5; GCI, 107.1; memory, 48.2; and motor, 53.8. The girls scored 2 to 4 percent higher than the boys on all scales. The scores were 2 to 3 percent lower in the children residing in Port Pirie than in those from the surrounding areas.

Comparison of the MSCA test results with the scores on the Bayley Mental Development Index, at the age of two years, showed that the GCI had the highest correlation (r = 0.58), whereas the motor scale had the lowest (r = 0.43). The MSCA motor scale was only moderately correlated with the Bayley Psychomotor Development Index (r = 0.28).

Table 1. Mean MSCA Scores at the Age of Four Years, According to Quartile of Blood Lead Concentration and Time of Blood Sampling.

Blood Lead Level*	Blood Sample								
	Antenatal (Average)	Delivery	Umbilical Cord	6 Mo	15 Mo	2 Yr	3 Yr	4 Yr	Integrated Postnatal Average
Mean blood lead level (μmol per liter)									
1	0.29	0.27	0.21	0.40	0.58	0.64	0.58	0.47	0.60
2	0.42	0.40	0.35	0.61	0.89	0.90	0.84	0.71	0.85
3	0.51	0.53	0.48	0.82	1.18	1.18	1.09	0.92	1.05
4	0.69	0.78	0.72	1.18	1.68	1.63	1.46	1.26	1.36
General cognitive index									
1	108.8	109.5	108.6	111.2	110.1	112.4	112.0	111.1	112.6
2	109.4	108.8	109.3	107.4	109.9	109.4	109.0	109.2	108.3
3	106.7	106.1	104.7	105.9	105.4	104.6	105.7	103.6	104.0
4	104.3	104.2	106.3	104.1	103.6	102.3	102.0	104.7	103.0
Perceptual-performance score									
1	58.4	58.0	57.7	59.2	58.5	59.5	59.0	58.8	59.7
2	57.9	57.9	57.7	57.0	58.5	58.3	58.3	58.7	58.1
3	56.5	56.2	55.2	55.8	56.1	55.7	56.7	54.9	55.6
4	55.2	55.3	57.1	55.6	54.6	54.1	53.6	55.2	54.1
Memory score									
1	48.2	49.1	49.3	49.8	49.2	50.9	51.1	50.7	50.2
2	49.4	49.5	48.6	47.6	49.4	49.0	48.3	48.3	48.1
3	48.0	47.7	47.7	48.0	47.1	47.3	47.3	46.8	46.9
4	47.3	46.9	47.2	47.2	47.1	45.6	45.9	47.0	46.3
Motor score									
1	54.4	54.9	54.5	55.6	55.2	55.6	55.9	55.0	56.0
2	54.4	53.9	54.3	53.6	54.0	55.4	54.2	55.0	54.3
3	53.9	53.9	52.9	53.4	53.5	51.9	53.7	52.0	52.1
4	52.5	52.4	53.2	52.9	52.8	52.2	51.5	52.7	52.8
No. of children	534	479	474	526	527	534	525	530	463

*The first quartile includes those with the lowest blood concentrations of lead and the fourth those with the highest concentrations.

Age-Specific Blood Lead Concentration and MSCA Scores

For each age of the children at which blood sampling was performed, the study population was subdivided into quartiles of blood lead concentration, each of which contained approximately 135 children. Variation in MSCA scores was examined in relation to these quartiles. At each age, there was a consistent inverse relation between blood lead concentration and MSCA scores.

This inverse relation had similar strength for the GCI, the memory

score, and the perceptual-performance score, with the mean values varying by approximately 10 percent between the highest and lowest quartiles of blood lead concentration. Table 1 shows that the range of mean scores was greater for blood lead concentrations measured postnatally than antenatally or at delivery and was greatest at the ages of two and three years. Since the verbal and quantitative scales are subsets of the GCI and the scores obtained on them varied only slightly with the blood lead concentration, they are not listed.

Figure 1 shows the variation in MSCA scores at four years of age in relation to blood lead concentration at three years of age — the age at which there was maximal variation in those scores according to quartile of blood lead concentration (Table 1). For each of the six scores, an inverse gradient extends across the full range of blood lead concentrations. Figure 1 depicts the unadjusted relation between blood lead concentration at the age of three years and MSCA score; the relations at 15 months and two years, as well as with the integrated postnatal blood lead concentration, resembled those shown in Figure 1.

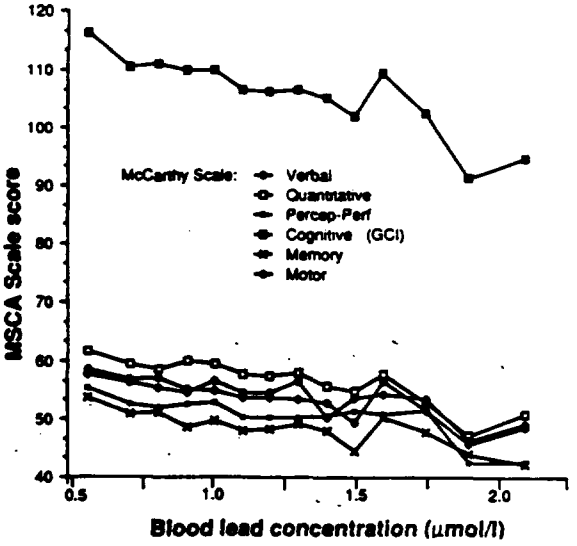

Figure 1. MSCA Scale Scores at the Age of Four Years, According to Blood Lead Concentration at Three Years of Age.

Relation of Other Covariates to MSCA Scores

For the covariates subsequently treated as potential confounders in multivariate analyses, their univariate relations with blood lead concentration and with the GCI and the perceptual-performance and memory scales are shown in Table 2. Many characteristics of the parents (including parental education, the mother's IQ and marital status, and the father's job) were strongly related to the MSCA scores, in the expected direction. Maternal age and the quality of the home environment were positively related to the scores. Obstetrical factors and neonatal characteristics were less strongly related, although the lower values (or the adverse findings) tended to be associated with low MSCA scores.

Regression Analyses of MSCA Scores and Blood Lead Concentration

Table 3 presents the results of simple and multiple linear regression analyses. The multivariate model contained almost all factors identified a priori as potential determinants of developmental abilities — irrespective of the variance in developmental score accounted for by the factor in multiple regression analysis. This approach errs toward overinclusion of covariates, but it does so because of the known difficulty of achieving adequate control of confounding factors in studies of lead and childhood development. The only factors excluded from the original list were two antenatal variables (bleeding during pregnancy and vitamin supplementation), which had no explanatory power in multivariate analysis and for which there were no a priori expectations of the effects on child mental development, and the Apgar score at one minute (which was supplanted by the Apgar score at five minutes). The fit of the linear models was not improved markedly by adding quadratic terms in blood lead concentration and in other continuous covariates (birth weight, maternal age, and HOME score).

The linearity observed with the logarithm of blood lead concentration accords with recent results from studies in schoolchildren in Edinburgh[9] and infants in Cincinnati.[25] Repetition of this analysis, using the untransformed blood lead concentration, did not alter the fit of the model.

The regression coefficients in Table 3 estimate the changes in MSCA score accompanying a 10-fold increase (i.e., one unit on a logarithmic scale) in the corresponding blood lead concentration. Thus, for example, an increase in the integrated postnatal blood lead concentration of from 0.25 to 2.50 μmol per liter would be accompanied by an estimated drop of 28.9 points in the GCI (last entry, first column), ignoring the confounding effects of other covariates. For an increase in the integrated postnatal blood lead concentration of from 0.50 to 1.50 μmol per liter, the expected drop in GCI would be $(\log_{10}3 \times 28.9) = 13.8$ points. After the adjustment for the covariates in the multiple regression analysis, the corresponding drops in GCI (see partial regression coefficients, Table 3) would be 15.0 points (for an increase in blood lead concentration from 0.25 to 2.50 μmol per liter) and 7.2 points (for from 0.50 to 1.50 μmol per liter). The figure of 7.2 points (95 percent confidence interval, 0.3 to 13.2) represents a decrease of approximately 7 percent in GCI score in a child with average values for the other covariates.

In simple regression analyses, blood lead concentration at every age was negatively related to the GCI and the perceptual-performance and memory scales (Table 3). These relations were weakest for the cord blood sample. In multiple regression analyses, the relations between antenatal and perinatal blood lead concentrations and these developmental outcomes

Table 2. Mean MSCA Scores for Covariates That May Confound the Relation between a Child's Ability and His or Her Exposure to Lead *

Covariate	Category	Integrated Mean Lead Level	General Cognitive Index		Perceptual Performance Scale		Memory Scale	
			Mean	P value (% variance)	Mean	P value (% variance)	Mean	P value (% variance)
		μmol/liter						
Sex	Male	0.92	105.7	0.058	55.6	0.002	47.5	0.10
	Female	0.92	108.3	(0.5)	58.0	(1.5)	48.8	(0.3)
Residence	Non-Pirie	0.70	109.4	0.06	57.6	0.31	49.6	0.035
	Pirie	1.00	106.4	(0.5)	56.7	(0.0)	47.7	(0.6)
Mother's education (yr)	<10	1.07	102.6	<0.001	54.8	0.003	46.0	0.005
	10	0.96	105.6	(3.2)	55.9	(2.1)	47.4	(1.9)
	11	0.86	107.8		57.7		48.5	
	≥12	0.83	113.2		59.5		50.8	
Mother's work site	Home	0.92	106.4	0.10	56.5	0.10	48.1	0.79
	External	0.92	108.9	(0.3)	57.9	(0.3)	48.4	(0.0)
Mother's marital status	Unmarried	1.13	99.6	<0.001	52.3	<0.001	44.7	0.001
	Married	0.90	107.8	(1.6)	57.3	(1.7)	48.5	(1.0)
Mother's age (yr)	≤21	1.11	102.3	<0.001	54.7	0.02	46.0	0.003
	22–29	0.90	107.3	(2.3)	57.0	(1.1)	48.1	(1.8)
	≥30	0.84	111.3		58.7		50.5	
Antenatal medication use	No	0.91	109.1	0.07	58.2	0.03	49.0	0.18
	Yes	0.93	106.4	(0.4)	56.4	(0.7)	47.9	(0.2)
Mother's IQ	<81	1.11	94.0	<0.001	48.6	<0.001	42.5	<0.001
	81–90	0.98	107.4	(9.1)	57.3	(9.6)	48.7	(6.2)
	91–100	0.88	107.8		57.4		48.3	
	>100	0.80	114.5		61.0		52.0	
	Not measured	0.95	105.5		55.9		47.0	
HOME score	<39	1.08	95.9	<0.001	50.8	<0.001	45.1	<0.001
	39–41	0.99	104.6	(16.0)	55.3	(13.5)	43.7	(9.1)
	42–44	0.92	109.3		58.4		47.0	
	45–47	0.79	110.5		58.9		48.5	
	>47	0.80	116.9		61.7		53.0	
Father's education (yr)	<10	0.96	104.8	<0.001	56.1	<0.001	46.2	0.002
	10	0.91	105.9	(5.9)	56.1	(6.8)	48.0	(2.3)
	11	0.91	108.3		58.0		48.3	
	≥12	0.82	114.6		60.8		51.4	
	Missing	1.09	99.6		51.3		46.6	
Father's work	Unemployed	1.11	97.3	<0.001	52.0	<0.001	43.3	<0.001
	Non-office	0.92	106.5		56.8		47.6	
	Office	0.83	113.8	(6.4)	59.9	(4.7)	51.7	(4.9)
	Unknown	1.13	101.1		52.9		45.6	
Delivery	Occipital	0.92	106.7	0.55	56.8	0.78	47.9	0.52
	Cesarean	0.95	109.1	(0.0)	57.7	(0.0)	48.7	(0.0)
	Other	0.90	107.7		56.9		48.9	
Apgar score at 5 min	9 or 10	0.90	105.5	0.23	56.4	0.55	47.1	0.14
	≤8	1.01	107.5	(0.1)	57.0	(0.0)	48.5	(0.2)
Oxygen use at birth	No	0.90	108.1	0.03	57.4	0.04	48.7	0.04
	Yes	0.99	104.8	(0.7)	55.6	(0.6)	47.0	(0.6)
Neonatal jaundice	No	0.91	107.4	0.59	57.1	0.60	48.4	0.98
	Yes	0.94	106.6	(0.0)	56.6	(0.0)	47.8	(0.0)
Birth weight (g)	<2500	1.06	99.3	0.02	53.0	0.01	44.0	0.17
	2500–2999	0.99	104.5	(1.3)	55.0	(1.6)	48.4	(0.4)
	3000–3499	0.93	107.1		56.6		48.3	
	≥3500	0.88	108.9		58.2		48.4	
Size for dates at birth	Small	1.01	100.7	0.10	53.6	0.01	44.3	0.08
	Appropriate	0.92	107.3	(0.5)	57.0	(1.6)	48.2	(0.6)
	Large	0.90	108.1		56.9		48.5	
Birth rank	First	0.95	106.7	0.62	56.5	0.68	48.4	0.44
	Second	0.91	107.0	(0.0)	57.3	(0.0)	47.6	(0.0)
	Subsequent	0.89	106.5		57.1		48.9	

*The P values indicate the global statistical significance of differences between the categories of each covariate, ignoring all other covariates. HOME denotes home observation for measurement of the environment.

were less strong. However, measures of postnatal blood lead concentration retained clear, negative, and predominantly statistically significant relations with the GCI. For these postnatal measures, including the integrated average value, the regression coefficients were approximately halved relative to their values in the simple regression. Thus, the covariates that were included were, in aggregate, positively confounded with blood lead concentration and accounted (either independently or through their association with expo-

sure to lead) for approximately half the apparent effect of blood lead concentration that was evident in simple regression analysis.

Repeated analysis including stratification according to sex did not significantly improve the fit, although the negative regression coefficient of blood lead concentration in relation to GCI score was slightly higher for girls than for boys. Repeated analysis restricted to children with blood lead concentrations below 1.21 μmol per liter (25 μg per deciliter) showed that the relation at such levels was as strong for this group of children as for the whole cohort (although statistical significance was decreased because of reductions in the range of exposure and the numbers of subjects). For the integrated postnatal average blood lead concentrations, the relation with GCI was actually stronger at values below 1.21 μmol per liter than overall. This could reflect either an actual greater dependence of GCI on blood lead concentration or less confounding by the other covariates, among children with less exposure.

When successive contractions of the age span of the integrated postnatal average blood lead concentration (i.e., spanning the periods from six months to, successively, the fourth, third, and second birthday) were substituted in the regression analyses, small progressive reductions occurred in each of the regression coefficients shown in the bottom row of Table 3. Thus, the integrated measure across the maximal age span (i.e., birth to the age of four years) showed the greatest inverse relation to developmental outcome.

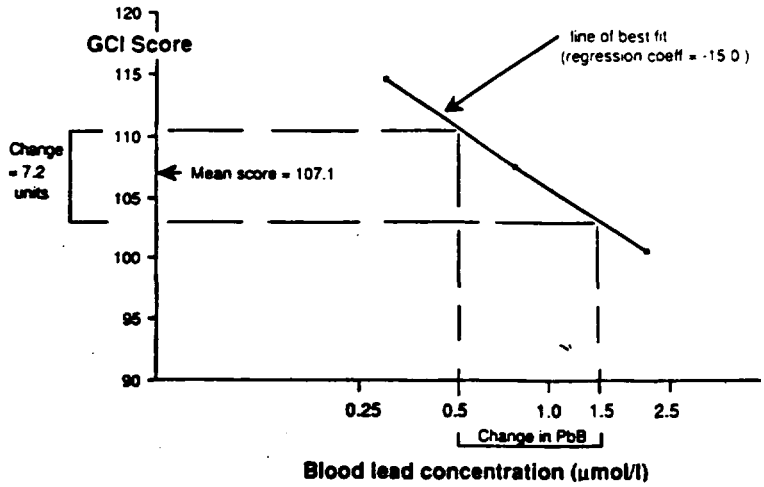

Figure 2. Linear Relation, as Estimated from Multiple Regression Analysis, between the Integrated Postnatal Average Blood Lead Concentration (Shown on a Logarithmic Scale) and the General Cognitive Index (GCI).

The estimated decrease in GCI associated with an increase in blood lead concentration from 0.50 to 1.50 μmol per liter is shown as an example; also see Discussion.

The estimated linear inverse relation between integrated postnatal blood lead concentration and GCI, within the range for which sufficient data were available (0.30 to 2.00 μmol per liter), and with use of the covariate-adjusted coefficient from Table 3, is shown in Figure 2. This fitted line indicates that a child with an average blood lead concentration of 1.50 μmol per liter during the first four years of life will have a GCI score approximately 7.2 points lower (95 percent confidence interval, 0.3 to 13.2) than a child with an average blood lead concentration of 0.50 μmol per liter.

Finally, the change in a child's average blood lead concentration between the first two years and the second two years of life was examined in relation to the change in (rank-ordered) measures of cognitive ability between the ages of two years (according to the Bayley Mental Developmental Index) and four years (according to the GCI). Such an analysis should reveal whether intellectual function at the age of four years is particularly influenced by recent blood lead levels. However, no relation was observed between changes in postnatal blood lead levels and changes

Table 3. Estimated Coefficients of Log Blood Lead Concentration from Simple and Multiple Regression Analyses of MSCA Scores at the Age of Four Years.*

Blood Sample	General Cognitive Index		Perceptual-Performance Scale		Memory Scale	
	Simple	Partial	Simple	Partial	Simple	Partial
	coefficient ±SE (P value)					
Antenatal (average)	−15.1±4.7 (0.001)	−1.8±5.7 (0.75)	−9.5±2.7 (<0.001)	−4.1±3.3 (0.22)	−4.8±2.7 (0.07)	2.0±3.3 (0.54)
Delivery	−10.4±3.9 (0.008)	−0.4±4.5 (0.93)	−5.1±2.3 (0.03)	0.2±2.7 (0.95)	−4.9±2.2 (0.03)	−0.4±2.6 (0.89)
Cord	−6.1±3.4 (0.08)	3.3±4.1 (0.42)	−3.0±2.0 (0.13)	1.6±2.4 (0.50)	−3.0±2.0 (0.12)	2.6±2.4 (0.27)
6 Mo	−15.1±3.8 (<0.001)	−8.5±4.4 (0.05)	−7.8±2.2 (<0.001)	−4.8±2.5 (0.06)	−4.9±2.2 (0.03)	−2.4±2.5 (0.34)
15 Mo	−14.3±3.8 (<0.001)	−3.5±4.8 (0.46)	−8.2±2.2 (<0.001)	−3.2±2.8 (0.26)	−5.3±2.2 (0.01)	−0.5±2.7 (0.87)
24 Mo	−25.8±4.3 (<0.001)	−11.1±5.4 (0.04)	−13.5±2.5 (<0.001)	−6.2±3.2 (0.05)	−13.4±2.4 (<0.001)	−7.3±3.1 (0.02)
36 Mo	−25.1±4.3 (<0.001)	−13.1±5.6 (0.02)	−13.6±2.5 (<0.001)	−7.7±3.3 (0.02)	−12.7±2.4 (<0.001)	−7.2±3.2 (0.27)
48 Mo	−20.1±4.1 (<0.001)	−5.5±5.1 (0.29)	−11.2±2.4 (<0.001)	−4.0±3.0 (0.18)	−10.3±2.3 (<0.001)	−4.1±3.0 (0.17)
Integrated postnatal average	−28.9±5.5 (<0.001)	−15.0±7.3 (0.04)	−15.1±3.2 (<0.001)	−8.3±4.1 (0.05)	−13.3±3.1 (<0.001)	−7.9±4.2 (0.06)

*The partial regression coefficients are from analyses incorporating all the covariates in Table 2. The P values are for assessments of the two-sided hypothesis that the estimates are not zero.

in intelligence scores. Futhermore, no such relation existed in the subset of children whose blood lead concentration increased with age, or when we used a regression model designed to control for regression to the mean by including the initial average blood lead concentration (i.e., that during the first two years) along with the difference for the two age periods.

Discussion

Our results corroborate recent findings in several epidemiologic studies,[1,9,25] each of which showed an inverse relation between blood lead concentration and early cognitive development. Among the children in the Port Pirie Cohort Study, there was an inverse relation between the average blood lead concentration in a sequence of samples obtained in early childhood and measures of cognitive functioning. This paper has described that relation at the age of four years; the inverse relation observed at the age of two years has been described elsewhere.[14]

In the Boston cohort study, the inverse relation remained statistically significant after adjustment for 26 covariates consisting of demographic, reproductive, obstetrical, neonatal, and postnatal variables (including maternal IQ and home environment).[1] In our study, 16 covariates that were thought to be potential confounders of the relation of interest were incorporated; thus, we included fewer antenatal and obstetrical variables in the multivariable model than did the Boston study.

In multivariate analyses that incorporate many covariates there is a possibility of "overcontrol."[2] If, for example, the area of residence affects mental development exclusively by determining the child's level of environmental exposure to lead, then it would be inappropriate to control for that covariate. However, while these interrelations remain unknown and controversy persists about whether exposure to lead affects mental development in childhood, inclusion of such covariates is prudent, even though it may cause any true adverse effect of lead to be underestimated.

The fact that the integrated postnatal (birth to the age of four years) average blood lead concentration showed the strongest inverse relation with the GCI score suggests that the adverse effect of exposure to lead on mental development is cumulative during early childhood. The relations of blood lead concentration at the age of four years to concurrent MSCA scores were much weaker in the multiple regression analyses than were those of blood lead concentrations at earlier ages. This finding and the evidence that a change in blood lead concentration between the first two years and the second two years of childhood does not affect development suggest that long-term exposure to lead is the primary determinant of risk of impaired mental development.

The inverse relation is most evident in relation to raised blood lead concentrations during the postnatal period. Within the cohort we studied, any adverse effects of elevations in maternal and fetal blood concentrations of lead are likely to have been overwhelmed by the much higher concentrations in the children because of their direct environmental exposure to high levels of lead during early childhood.

This phase of the Port Pirie Cohort Study indicates that a group of children with an average blood lead concentration of 1.50 μmol per liter will have a decrease in mean GCI score of approximately 7 percent, as compared with children with an average blood lead concentration of 0.50 μmol per liter. The latter blood lead concentration would be typical of a population with little environmental exposure to lead. In public health terms — and assuming that a reduction in mean GCI score reflects a shift in score distribution rather than a change in the shape of that distribution — a downward shift of the distribution of GCI scores of this magnitude represents about half a standard deviation (1 SD equals 15 GCI points[15]). Hence, an additional 15 percent of the children with high exposure to lead could be considered to have developmental delay on the basis of the criterion that a developmental score more than 1 SD below the mean merits clinical attention.

The results of this analysis and those of the earlier analysis of the children at the age of two years[14] suggest that increased exposure to lead results in a developmental deficit, not just developmental delay. The current analysis indicates that cumulative environmental exposure to lead in early childhood is critical in affecting subsequent mental development. Furthermore, the findings of the Port Pirie and Boston cohort studies, which collectively investigated a wide range of blood lead concentrations in very young children, indicate that there may be no clear threshold below which an adverse effect on mental development does not occur.

This cohort study indicates that a raised blood lead concentration in early childhood has an independent deleterious effect on mental development as evaluated at the age of four years. This effect was not accounted for by the known and measurable influences of obstetrical, parental, family, and social environmental factors on mental development. However, because of the intrinsic difficulty of defining and controlling confounding factors when studying the relation between blood lead levels and mental development, causal inferences must be made only with circumspection. The fact that the effect has been observed longitudinally at the ages of two and four years within this cohort and that it is stronger at four years suggests that any adverse effect of lead is cumulative and may result in long-term impairment in development rather than a delay in development.

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